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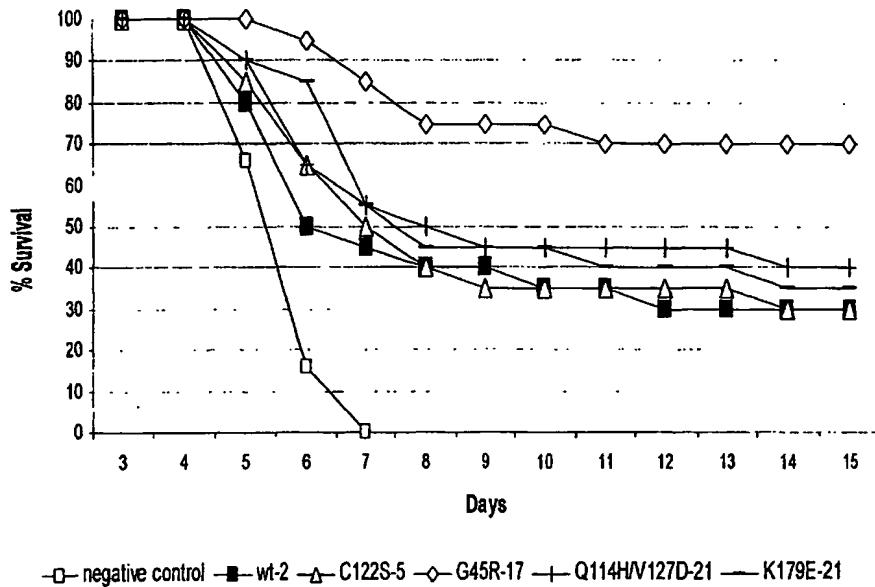
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Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

[Continued on next page]

(54) Title: METHOD FOR PROVIDING NATURAL THERAPEUTIC AGENTS WITH HIGH THERAPEUTIC INDEX



-□- negative control -■- wt-2 -△- C122S-5 -◇- G45R-17 -+ Q114H/V127D-21 — K179E-21

WO 2004/042394 A3

(57) Abstract: Methods for identifying and providing new therapeutic agent(s) by selecting at least one polypeptide encoded by a natural allelic variant of one preselected gene having a therapeutic potential; determining the therapeutic index of the selected polypeptide(s) and retaining as therapeutic agent(s) those polypeptide(s) whose therapeutic index is higher than that of a reference agent. The therapeutic indices of antiviral, anti-proliferative and immunomodulatory activities as well as toxicity are determined for members of the IFN $\alpha$  gene family.



(88) Date of publication of the international search report:  
15 July 2004

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/13695

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 G01N33/50 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, COMPENDEX, MEDLINE, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ORTALDO J R ET AL: "EFFECTS OF SEVERAL SPECIES OF HUMAN LEUKOCYTE INTERFERON ON CYTO TOXIC ACTIVITY OF NATURAL KILLER CELLS AND MONOCYTES"          INTERNATIONAL JOURNAL OF CANCER,          vol. 31, no. 3, 1983, pages 285-290,          XP008016137          ISSN: 0020-7136          the whole document</p> <p>-----</p> <p style="text-align: center;">-/-</p>	1-22

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed Invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed Invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the International search

8 June 2004

Date of mailing of the International search report

06 MAY 2004

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/13695

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PESTKA S: "The human interferons--from protein purification and sequence to cloning and expression in bacteria: before, between, and beyond." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS. UNITED STATES 15 FEB 1983, vol. 221, no. 1, 15 February 1983 (1983-02-15), pages 1-37, XP008016138 ISSN: 0003-9861 page 23, right-hand column, line 14 - page 26, right-hand column, line 14 table VI</p> <p>-----</p>	1-22
X	<p>SPERBER S J ET AL: "ANTI-HIV-1 ACTIVITY OF RECOMBINANT AND HYBRID SPECIES OF INTERFERON-ALPHA" JOURNAL OF INTERFERON RESEARCH, MARY ANN LIEBERT, INC., NEW YORK, NY, US, vol. 12, 1992, pages 363-368, XP001038692 ISSN: 0197-8357 the whole document</p> <p>-----</p>	1-22
X	<p>EVINGER M ET AL: "ANTI PROLIFERATIVE AND ANTI VIRAL ACTIVITIES OF HUMAN LEUKOCYTE INTERFERONS" ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 210, no. 1, 1981, pages 319-329, XP008016158 ISSN: 0003-9861 page 328, left-hand column, line 26 - right-hand column, line 32</p> <p>-----</p>	1-22
X	<p>WO 02/086156 A (ESCARY JEAN-LOUIS ;GENODYSEE (FR)) 31 October 2002 (2002-10-31) the whole document</p> <p>-----</p>	15-22
X	<p>WO 02/079249 A (ESCARY JEAN-LOUIS ;GENODYSEE (FR)) 10 October 2002 (2002-10-10) the whole document</p> <p>-----</p>	15-22

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/13695

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2.  Claims Nos.: 15-22 (in part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1 and 3-14 (in as far as they relate to in vivo activity tests) are directed to a method of treatment and/or a diagnostic method of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Claims Nos.: 1,3-14 (in part: i.e. not searched in as far as relating to in vivo activity tests)

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

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Continuation of Box I.2

Claims Nos.: 15-22 (in part)

Present claims 15-22 relate to a therapeutic agent defined or the use thereof by reference to a desirable characteristic or property, namely being obtainable by the method according to any of one of claims 1 to 14.

The claims cover all therapeutic agents having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such therapeutic agents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the therapeutic agents by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the IFN-alpha therapeutic agents disclosed in the experimental section, examples 1-5.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/13695

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 02086156	A	31-10-2002	FR CA WO EP NO	2823764 A1 2444235 A1 02086156 A2 1390543 A2 20034692 A		25-10-2002 31-10-2002 31-10-2002 25-02-2004 19-12-2003
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WO 02079249	A	10-10-2002	FR CA WO EP	2822845 A1 2442775 A1 02079249 A2 1379695 A2		04-10-2002 10-10-2002 10-10-2002 14-01-2004
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